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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07H 17/08, A61K 31/70

A1

(11) International Publication Number: **WO 99/21869**

(43) International Publication Date: 6 May 1999 (06.05.99)

(21) International Application Number: PCT/JP98/04876

(22) International Filing Date: 28 October 1998 (28.10.98)

(30) Priority Data:
9/296822 29 October 1997 (29.10.97) JP

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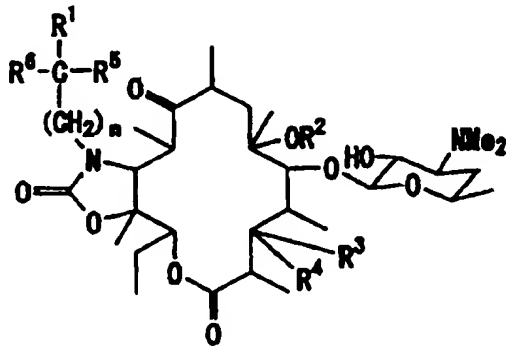
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: ERYTHROMYCIN A, 11,12–CARBAMATE DERIVATIVES



(I)

(57) Abstract

An erythromycin A derivative represented by formula (I) wherein n is an integer of 1 to 7, $R^1$ is a group represented by the formula: $-SO_2N(-R^7)-R^8$ or $N-(R^{10})SO_2R^9$, $R^2$ is a hydrogen atom, an alkyl group or a cinnamyl group, $R^3$ is a group represented by the formula: $-OCO-CH_2-R^{11}$, $-OCO-R^{11}$, $-OCO-NH-R^{11}$, $-O-R^{11}$ or $-OCO-O-R^{11}$, $R^4$ is a hydrogen atom, or $R^3$ and $R^4$ together form an oxo group, and $R^5$ and $R^6$ are each a hydrogen atom or an alkyl group, or a pharmaceutically acceptable salt thereof has a strong antibacterial activity against not only known erythromycin–sensitive bacteria but also erythromycin–resistant bacteria.

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# DESCRIPTION

## ERYTHROMYCIN A, 11,12-CARBAMATE DERIVATIVES

### TECHNICAL FIELD

The present invention relates to novel derivatives of antibiotic erythromycin A.

### BACKGROUND ART

Erythromycin A is an antibiotic clinically widely used as an agent for treating infectious diseases caused by Gram-positive bacteria, mycoplasmas, etc. However, erythromycin A is decomposed by the gastric acid due to instability to acids, and thereby has a drawback of no constancy of movement in the body. Hitherto many erythromycin A derivatives have been prepared for the purpose of the improvement of the biological or pharmacological properties. For example, it is reported that 6-O-methylerythromycin A derivatives have an improved stability to acids and have a superior in vivo antibacterial activity in comparison with erythromycin A when administered orally (U.S. Patent No. 4331803). Recently, it is also reported that 11,12-cyclic carbamate derivatives are prepared from 6-O-methylerythromycin A as a starting material with the aim of expansion of antibacterial spectrum as well as stability to acids (EP. patent No. 487411 and US. Patent No. 4742049). In addition, the antibacterial activities

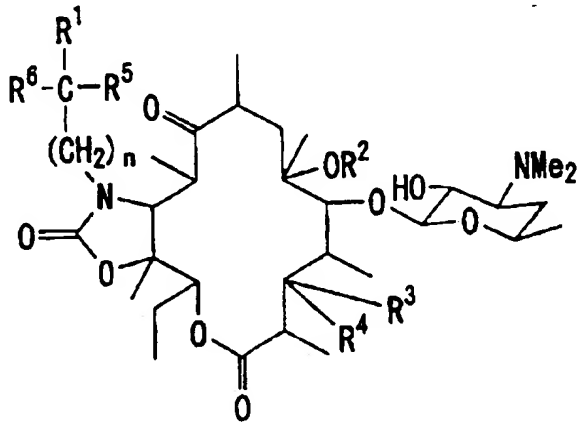
of the ester derivatives at the 3-position are also reported by some of the present inventors (EP. patent No.619320).

An object of the present invention is to provide post-generational macrolide antibiotics having a strong antibacterial activity against not only known erythromycin-sensitive bacteria but also erythromycin-resistant bacteria which recently are showing a tendency to increase.

DISCLOSURE OF THE INVENTION

The present inventors have found that the compounds which can be produced by introducing a sulfonamide group onto the alkyl group attached to the nitrogen atom of the 11,12-cyclic carbamate of erythromycin A and converting 3-position of the erythromycin A have a strong antibacterial activity against not only erythromycin-sensitive bacteria but also erythromycin-resistant bacteria, and thus the present invention has been accomplished.

The present invention relates to an erythromycin A derivative represented by the formula:



wherein n is an integer of 1 to 7,

$R^1$ is a group represented by the formula:

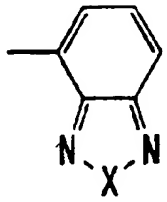
$$-SO_2N(-R^7)-R^8$$

wherein $R^7$ is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a phenyl group, a phenyl group substituted by a nitro group or an alkoxy group having 1 to 3 carbon atoms, a pyridyl group, a pyridyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a halogen atom; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group and an amino group substituted by an alkyl group having 1 to 6 carbon atoms, a quinolyl group, or a quinolyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a halogen atom; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group and an amino group substituted by an alkyl group having 1 to 6 carbon atoms, $R^8$ is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, or

a group represented by the formula:

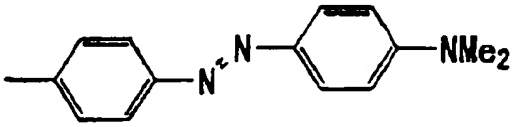
$-N-(R^{10})SO_2R^9$

wherein $R^9$ is an alkyl group having 1 to 6 carbon atoms, a dibenzofuranyl group, a thienyl group, a thienyl group substituted by a group selected from the group consisting of a pyridyl group; an isoxazolyl group; a pyrimidinyl group and a pyrimidinyl group substituted by an alkoxy group having 1 to 6 carbon atoms or an alkylthio group having 1 to 6 carbon atoms, an isoxazolyl group, an isoxazolyl group substituted by 1 or 2 alkyl groups having 1 to 6 carbon atoms, an imidazolyl group, an imidazolyl group substituted by 1 to 3 alkyl groups having 1 to 6 carbon atoms, a benzothienyl group, a benzothienyl group substituted by 1 to 5 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms and a halogen atom, a thiazolyl group, a thiazolyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; an amino group and an acetamino group, an imidazo[2,1-b]thiazolyl group, an imidazo[2,1-b]thiazolyl group substituted by 1 to 3 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms and a halogen atom, a phenylalkyl group having 7 to 10 carbon atoms, a quinolyl, a pyridyl, a naphthyl group, a naphthylalkyl group having 11 to 15 carbon atoms, a dimethylamino-naphthyl group, a group represented by the formula:



wherein X is -O- or -S-,

a group represented by the formula:



a phenyl group, a phenyl group substituted by 1 to 5 members selected from the group consisting of a hydroxyl group; a methylsulfonyl group; an alkyl group having 1 to 6 carbon atoms; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group; a dimethylamino group; an acetylamino group; a pyridyl group; a trifluoromethyl group; a trifluoromethoxy group and a halogen atom, a pyridyl group, a pyridyl group substituted by 1 or 2 members selected from the group consisting of a hydroxyl group; an alkyl group having 1 to 6 carbon atoms; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group; a dimethylamino group; an acetylamino group; a pyridyl group; a trifluoromethyl group; a trifluoromethoxy group and a halogen atom, a quinolyl group, or a quinolyl group substituted by 1 or 2 members selected from the group consisting of a hydroxyl group; an alkyl group having 1 to 6 carbon atoms; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group; a dimethylamino group; an acetylamino group; a

pyridyl group; a trifluoromethyl group; a trifluoromethoxy group and a halogen atom, and $R^{10}$ is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms,

$R^2$ is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or a cinnamyl group,

$R^3$ is a group represented by the formula:

$$-OCO-CH_2-R^{11}$$

a group represented by the formula:

$$-OCO-R^{11}$$

a group represented by the formula:

$$-OCO-NH-R^{11}$$

a group represented by the formula:

$$-O-R^{11}$$

or a group represented by the formula:

$$-OCO-O-R^{11}$$

wherein $R^{11}$ is a pyridylmethyl group, a methylthiomethyl group, a quinolyl group, a phenyl group, a phenyl group substituted by 1 to 5 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a nitro group; an alkoxy group having 1 to 3 carbon atoms and a halogen atom, a pyridyl group, or a pyridyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a nitro group; an alkoxy group having 1 to 3 carbon atoms and a halogen atom,

$R^4$ is a hydrogen atom, or $R^3$ and $R^4$ together form an oxo group, and

$R^5$ and $R^6$ are the same or different, and are each a

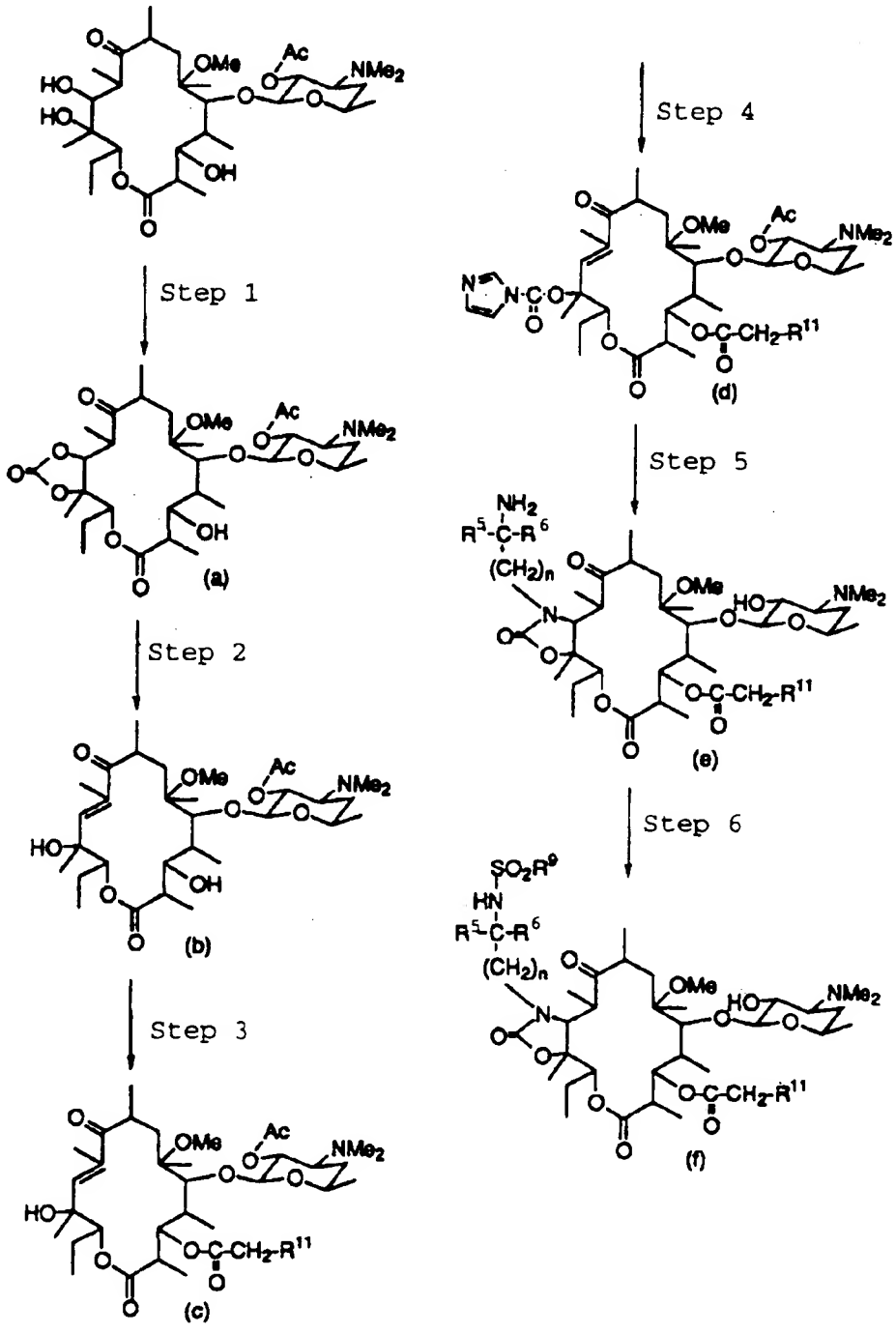
hydrogen atom or an alkyl group having 1 to 6 carbon atoms, or a pharmaceutically acceptable salt thereof.

In the present invention, examples of the alkyl group having 1 to 6 carbon atoms are a methyl group, an ethyl group, a propyl group, a butyl group, a 3-methylbutyl group and a cyclohexyl group; examples of the alkoxy group having 1 to 3 carbon atoms are a methoxy group, an ethoxy group, a propoxy group and an isopopoxy group; and the halogen atom refers to a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

The pharmaceutically acceptable salt refers to a salt used in chemotherapy or prophylaxis of bacterially infectious diseases, for example, a salt with acetic acid, propionic acid, butyric acid, formic acid, trifluoroacetic acid, maleic acid, tartaric acid, citric acid, stearic acid, succinic acid, ethylsuccinic acid, lactobionic acid, gluconic acid, glucoheptonic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, laurylsulfuric acid, malic acid, aspartic acid, glutaminic acid, adipic acid, cysteine, N-acetylcysteine, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, hydroiodic acid, nicotinic acid, oxalic acid, picric acid, thiocyanic acid, undecanoic acid, polyacrylate or carboxyvinyl polymer.

The compounds of the present invention can be

prepared, for example, according to the following reaction scheme.



Step (1); 2'-O-Acetyl-5-O-desosaminyl-6-O-methylerythronolide A described in US patent No. 5,523,399 is reacted with triphosgene in an inert solvent in the presence of pyridine under ice-cooling to give a compound of Formula (a). Examples of the inert solvent to be used here are dichloromethane, dichloroethane, acetone and tetrahydrofuran.

Step (2); The compound of Formula (a) is treated with a base in an inert solvent at a temperature of from room temperature to 120°C to give a compound of Formula (b). Examples of the inert solvent to be used here are N,N-dimethylformamide, dimethyl sulfoxide, N-methylpiperidone, tetrahydrofuran and a mixture thereof, and examples of the base to be used here are 1,1,3,3-tetramethylguanidine and potassium carbonate.

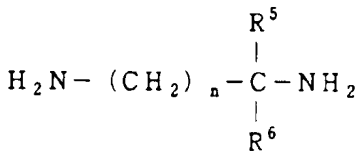
Step (3); The compound of Formula (b) is treated with a reagent of the following formula:

$R^{11}$-$CH_2COOH$

wherein $R^{11}$ is as defined above, and an activating agent thereof in an inert solvent in the presence of a base such as 4-dimethylaminopyridine at a temperature of from -30°C to 30°C to give a compound of Formula (c). Examples of the activating agent to be used herein are 1,3-dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and pivaloyl chloride. Examples of the inert solvent to be used here are dichloromethane, dichloroethane, acetone, pyridine, ethyl acetate and tetrahydrofuran.

Step (4); The compound of Formula (c) is reacted with 1,1'-carbonyldiimidazole in an inert solvent under the presence of a base such as sodium hydride to give a compound of Formula (d). The inert solvent is the same as used in Step (3).

Step (5); The compound of Formula (d) is reacted in an inert solvent with an amine compound of the following formula:



wherein n, $R^5$ and $R^6$ are as defined above, and then is deprotected at the 2'-position by an ordinary methanolysis to give a compound of Formula (e). Examples of the inert solvent to be used here are acetonitrile, tetrahydrofuran, N,N-dimethylformamide, dioxane, ethyl acetate, N-methylpyrrolidone, a mixture of the solvent and water and a mixture thereof.

Step (6); The compound of Formula (e) is reacted with a reagent of the following formula:

$R^9SO_2Cl$

wherein $R^9$ is as defined above, in an inert solvent in the presence of a base such as pyridine, to give a compound of Formula (f) which is a compound of the present invention. The inert solvent is the same as used in Step (3).

The compounds of the present invention can be administered orally or parenterally in the dosage form

such as, for example, tablets, capsules, powders, troches, ointments, suspensions, suppositories and injections, all of which can be prepared according to conventional preparation techniques. The dose of the present compounds for treating an adult is from 100 to 1000 mg/day in single or several divided doses. This dose can be increased or decreased depending on the age, body weight and conditions of the patient.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail by the following Examples and a Test Example.

Reference Example 1

Synthesis of 11-(2-aminoethyl)amino-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) To a solution of 70.0 g (77 mmol) of 10,11-anhydro-2',4"-di-O-acetyl-12-O-imidazolylcarbonyl-6-O-methylerythromycin A described in European Patent No. 638584 in 1 L of acetonitrile was added 30.0 ml (0.23 mol) of ethylenediamine at room temperature, followed by stirring overnight. The reaction solution was evaporated under reduced pressure, and the residue was dissolved in 1 L of methanol and refluxed under heating for 4 hours. After evaporation of the solvent, purification by silica gel column chromatography (chloroform : methanol : aqueous ammonia =20:1:0.1) gave

67.0 g (yield: 97 %) of 4"-O-acetyl-11-(2-aminoethyl)-amino-11-deoxy-6-O-methylerythromycin A 11,12-cyclic carbamate.

(2) A solution of 20 g (24 mmol) of the compound obtained in the above (1) in 100 ml of 1N aqueous hydrochloric acid solution was stirred at 70°C for an hour. The mixture was cooled to room temperature, and extracted with chloroform to remove the cladinose. The aqueous layer was made basic with an aqueous sodium hydroxide solution, extracted with chloroform and washed with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was crystallized from 50 ml of ether to give 9.8 g (yield: 63 %) of the title compound.

SIMS m/z: 658 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm): 2.25 (s, 6H, $NMe_2$), 3.00 (s, 3H, 6-OMe), 4.40 (d, 1H, J=7.3 Hz, H-1'), 5.22 (dd, 1H, J=11.0, 2.4 Hz, H-13).

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 40.3 ($NMe_2$), 49.6 (6-OMe), 106.9 (C1'), 157.9 (11,12-carbamate), 175.7 (C1), 215.6 (C9).

Example 1

<u>11-[2-[(4-Acetaminophenyl)sulfonylamino]-ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

(1) To a solution of 1.38 g (2.1 mmol) of the compound obtained in Reference Example 1 in 30 ml of a mixture of methylene chloride and pyridine was added 0.59 g (2.5 mmol) of p-acetamidobenzenesulfonyl chloride under ice-cooling, followed by stirring for 1.5 hours at room temperature. The reaction solution was diluted with ethyl acetate, and washed with an aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution respectively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 2.07 g of 11-[2-[(4-acetaminophenyl)sulfonylamino]-ethyl]amino-11-deoxy-5-O-desosaminyl-6-O-methyl-erythronolide A 11,12-cyclic carbamate.

(2) 2.07 g of the compound obtained in the above (1) was dissolved in 20 ml of acetone, and 0.3 ml (3.2 mmol) of acetic anhydride was added thereto at room temperature, followed by stirring overnight. After the reaction, the reaction solution was diluted with ethyl acetate, and washed with a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution respectively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 1.90 g of a 2'-O-acetyl compound.

(3) To a solution of 1.00 g (1.1 mmol) of the compound obtained in the above (2) in 20 ml of methylene chloride were successively added 0.58 g (3.3 mmol) of 2-

pyridylacetate hydrochloride, 0.64 g (3.3 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 0.14 g (1.1 mmol) of 4-dimethylaminopyridine under ice-cooling, followed by stirring at room temperature overnight. After the reaction, the reaction solution was diluted with ethyl acetate, and washed with an aqueous sodium hydroxide solution, a saturated aqueous ammonium chloride solution and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 1.06g of the residue, which was then dissolved in 20 ml of methanol and stirred at room temperature overnight. After the reaction, the solvent was evaporated under reduced pressure, and purification by silica gel column chromatography (chloroform : methanol : aqueous ammonia =15:1:0.1) gave 0.85 g (yield: 78 %) of the title compound.

IonSprayMS m/z: 974.5 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm): 2.03 (s, 3H, -COC<u>H</u>$_3$), 2.28 (s, 6H, $NMe_2$), 2.52 (s, 3H, 6-OMe), 3.95 and 3.98 (each d, each 1H, $J_{gem}$=16.2 Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.07 (d, 1H, J=7.3 Hz, H-1'), 4.91 (d, 1H, J=11.0 Hz, H-3), 4.92 (dd, 1H, J=11.2, 1.1 Hz, H-13), 5.49 (brs, 1H, -N<u>H</u>$SO_2$-), 8.14 (brs, 1H, -N<u>H</u>Ac).

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm): 24.3 (-CO<u>C</u>$H_3$), 40.3 ($NMe_2$), 49.7 (6-OMe), 103.4 (C1'), 157.5 (11,12-carbamate), 168.7 (-<u>C</u>O$CH_3$), 171.1 (-<u>C</u>O$CH_2$[2-

Pyridine]), 175.0 (C1), 215.7 (C9).

Example 2

11-[2-[(4-Acetaminophenyl)sulfonylamino]-ethyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

To a solution of 0.87 g (0.97 mmol) of the compound obtained in Example 1(2) in 18 ml of methylene chloride were successively added 0.69 ml (9.7 mmol) of dimethyl sulfoxide, 0.56 g (2.9 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 0.56 g (2.9 mmol) of pyridinium trifluoroacetate under ice-cooling, followed by stirring at room temperature overnight. After the reaction, the reaction solution was diluted with ethyl acetate, and washed with an aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 0.99 g of the residue, which was then dissolved in 20 ml of methanol and stirred at room temperature overnight. After the reaction, the solvent was evaporated under reduced pressure, and purification by silica gel column chromatography (chloroform : methanol : aqueous ammonia =15:1:0.1) gave 0.55 g (yield: 66 %) of the title compound.

IonSprayMS m/z: 853.5 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.20 (s, 3H, -NHCOC$\underline{H_3}$),

2.26 (s, 6H, $NMe_2$), 2.54 (s, 3H, 6-OMe), 3.83 (q, J=6.7 Hz, H-2), 4.22 (d, 1H, J=8.6 Hz, H-5), 4.27 (d, 1H, J=7.3 Hz, H-1'), 4.88 (dd, 1H, J=11.0, 2.4 Hz, H-13), 5.77 (brt, 1H, J=5.5 Hz, $-N\underline{H}SO_2-$), 8.00 (s, 1H, $-N\underline{H}COCH_3$)

$^{13}C$-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 24.6 ($-NHCO\underline{C}H_3$), 40.2 ($NMe_2$), 49.7 (6-OMe), 104.0 (C1'), 158.0 (11,12-carbamate), 168.8 ($-NH\underline{C}OCH_3$), 170.1(C1), 203.5 (C3), 216.4 (C9).

Example 3

<u>11-[2-[(2-Nitrophenyl)sulfonylamino]ethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

(1) Following the same procedures as in Example 1(1) and (2) using 1.57 g (2.4 mmol) of the compound obtained in Reference Example 1 and 0.63 g (2.8 mmol) of 2-nitrobenzenesulfonyl chloride, there was obtained 2.16 g of the 2'-O-acetyl compound.

(2) Following the same procedure as in Example 1(3) using 1.03 g (1.2 mmol) of the compound obtained in the above (1), there was obtained 0.66 g (yield: 59 %) of the title compound.

SIMS m/z: 962 $[M+H]^+$

$^1H$-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.99 (s, 3H, 6-OMe), 3.92 and 3.96 (each d, each 1H, $J_{gem}$=16.2 Hz, $-C\underline{H}_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 5.02 (d, 1H, J=11.0 Hz, H-3), 5.06 (dd, 1H,

J=11.0, 2.1 Hz, H-13), 6.26 (brs, 1H, -NHSO$_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.3 (6-OMe), 103.5 (C1'), 157.5 (11,12-carbamate), 170.4 (-COCH$_2$[2-Pyridine]), 174.8 (C1), 215.8 (C9).

Example 4

11-[2-[(2-Nitrophenyl)sulfonylaminolethyl]-amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 2 using 1.06 g (1.2 mmol) of the compound obtained in Example 3(1), there was obtained 0.88 g (yield: 88 %) of the title compound.

IonSprayMS m/z: 841.4 $[M+H]^+$

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.58 (s, 3H, 6-OMe), 3.84 (q, J=6.7 Hz, H-2), 4.24 (d, 1H, J=9.0 Hz, H-5), 4.27 (d, 1H, J=7.3Hz, H-1'), 4.96 (dd, 1H, J=10.8, 2.3 Hz, H-13)

Example 5

11-[2-[[1-(5-Dimethylamino)naphthyl]sulfonyl-aminolethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedures as in Example 1(1) and (2) using 1.44 g (2.2 mmol) of the compound obtained in Reference Example 1 and 0.71 g (2.6 mmol) of 1-dimethylaminonaphthalene-5-sulfonyl chloride,

there was obtained 2.18 g of the 2'-O-acetyl compound.

(2) Following the same procedure as in Example 2(3) using 1.02 g (1.1 mmol) of the compound obtained in the above (1), there was obtained 0.95 g (yield: 86 %) of the title compound.

IonSprayMS m/z: 1010.6 $[M+H]^+$

$^1$H-NMR(300MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.71 (s, 3H, 6-OMe), 2.86(s, 6H, [Naphthalene]-$NMe_2$), 3.95 (s, 2H, -$CH_2$[2-Pyridine]), 4.05 (d, 1H, J=7.3 Hz, H-1'), 4.99 - 5.06 (m, 2H, H-3 and H-13), 6.23 (brt, 1H, J=6.0 Hz, -$NHSO_2$-).

Example 6

11-[2-[[1-(5-Dimethylamino)naphthyl]sulfonyl-aminolethyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 2 using 1.19 g (1.3 mmol) of the compound obtained in Example 5(1), there was obtained 0.91 g (yield: 79 %) of the title compound.

SIMS m/z: 889 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.44 (s, 3H, 6-OMe), 2.88 (s, 6H, [Naphthalene]-$NMe_2$), 3.83 (q, J=6.7Hz, H-2), 4.20 (d, 1H, J=8.5Hz, H-5), 4.27 (d, 1H, J=7.3 Hz, H-1'), 4.91 (dd, 1H, J=11.0, 2.4 Hz, H-13), 6.11 (brt, 1H, J=5.5Hz, -$NHSO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 45.4 ([Naphthalene]-$NMe_2$), 49.6 (6-OMe), 103.9 (C1'),

157.9 (11,12-carbamate), 170.0 (C1), 203.4 (C3), 216.3 (C9).

Example 7

11-[2-(Benzo-2,1,3-thiadiazole-4-sulfonyl-amino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedures as in Example 1(1) and (2) using 1.21 g (1.8 mmol) of the compound obtained in Reference Example 1 and 0.52 g (2.2 mmol) of benzo-2,1,3-thiadiazole-4-sulfonyl chloride, there was obtained 1.75 g of the 2'-O-acetyl compound.

(2) Following the same procedure as in Example 1(3) using 0.85 g (0.95 mmol) of the compound obtained in the above (1), there was obtained 0.78 g (yield: 85 %) of the title compound.

SIMS m/z: 975 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.91 (s, 3H, 6-OMe), 3.92 and 3.98 (each d, each 1H, $J_{gem}$=16.1 Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.06 (d, 1H, J=7.4 Hz, H-1'), 5.01 (d, 1H, J=11.2 Hz, H-3), 5.04 (dd, 1H, J=11.0, 2.1 Hz, H-13), 6.28 (brs, 1H, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.2 (6-OMe), 103.6 (C1'), 157.3 (11,12-carbamate), 170.4 (-<u>C</u>$OCH_2$[2-Pyridine]), 174.8 (C1), 215.7 (C9).

Example 8

11-[2-(Benzo-2,1,3-thiadiazole-4-sulfonylamino)ethylamino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 2 using 0.85 g (0.94 mmol) of the compound obtained in Example 7(1), there was obtained 0.67 g (yield: 84 %) of the title compound.

SIMS m/z: 854 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.51 (s, 3H, 6-OMe), 3.83 (q, J=6.7 Hz, H-2), 4.22 (d, 1H, J=9.2 Hz, H-5), 4.27 (d, 1H, J=7.3 Hz, H-1'), 4.93 (dd, 1H, J=11.0, 2.4 Hz, H-13), 6.15 (brs, 1H, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 24.6 (-NHCO<u>C</u>$H_3$), 40.2 ($NMe_2$), 49.8 (6-OMe), 104.0 (C1'), 157.3 (11,12-carbamate), 170.0 (C1), 203.4 (C3), 216.3 (C9).

Example 9

11-[2-[(8-Quinolyl)sulfonylamino]ethylamino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedures as in Example 1(1) and (2) using 2.02 g (3.1 mmol) of the compound obtained in Reference Example 1 and 0.84 g (3.7 mmol) of quinoline-8-sulfonyl chloride, there was obtained 3.08 g of the 2'-O-acetyl compound.

(2) Following the same procedure as in Example 2 using 3.08 g of the compound obtained in the above (1), there was obtained 2.45 g (yield: 94 %) of the title compound.

IonSpray MS m/z: 847.4 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.43 (s, 3H, 6-OMe), 3.80 (q, J=7.0 Hz, H-2), 4.18 (d, 1H, J=8.8 Hz, H-5), 4.27 (d, 1H, J=7.4 Hz, H-1'), 4.93 (dd, 1H, J=10.6, 2.4 Hz, H-13), 6.73 (brt, 1H, J=6.4 Hz, $-N\underline{H}SO_2-$)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 49.6 (6-OMe), 104.0 (C1'), 157.4 (11,12-carbamate), 169.4(C1), 203.8 (C3), 216.0 (C9).

Example 10

<u>11-[2-[(8-Quinolyl)sulfonylamino]ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

(1) To a solution of 53.6 g (0.09 mol) of 2'-O-acetyl-5-O-desosaminyl-6-O-methylerythronolide A in 500 ml of methylene chloride was added 54.9 ml (0.70 mol) of pyridine. 16.8 g (0.06 mol) of triphosgene was added to the mixture under ice-cooling, followed by stirring at room temperature for 2 hours. After the reaction, water was added to the reaction mixture under ice-cooling to decompose the excess triphosgene, and the mixture was diluted with chloroform and washed with water and a saturated aqueous sodium chloride solution

successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 56.0 g of the 11,12-cyclic carbonate compound.

(2) To a solution of 56.0 g of the compound obtained in the above (1) in 500 ml of N,N-dimethylformamide was added 23.7 ml (0.23 mol) of 1,1,3,3-tetramethylguanidine, followed by stirring at 100°C for 3 hours. After the reaction, the reaction solution was diluted with ethyl acetate and washed with distilled water and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 50.27 g of 10,11-anhydro-2'-O-acetyl-5-O-desosaminyl-6-O-methylerythronolide A.

(3) Following the same procedure as in Example 2(3) using 50.3 g (0.08 mol) of the compound obtained in the above (2), there was obtained 41.95 g of 10,11-anhydro-2'-O-acetyl-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A.

(4) To a solution of 31.0 g (0.04 mol) of the compound obtained in the above (3) in a mixture of 180 ml of N,N-dimethylformamide and 120 ml of tetrahydrofuran were successively added 20.6 g (0.13 mol) of carbonyldiimidazole and 3.38 g (0.08 mol) of sodium hydride under ice-cooling, followed by stirring under ice-cooling for 40 minutes. After the reaction,

the reaction solution was diluted with ethyl acetate and washed with distilled water and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 32.7 g of 10,11-anhydro-2'-O-acetyl-12-O-imidazolylcarbonyl-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A.

(5) To a solution of 11.5 g (14.6 mmol) of the compound obtained in the above (4) in 100 ml of acetonitrile was added 9.8 ml (0.15 mol) of ethylenediamine, followed by stirring for 2 days. After the reaction, the reaction solution was diluted with ethyl acetate and washed with distilled water and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in 100 ml of methanol, followed by stirring at room temperature overnight. After the reaction, the reaction solution was evaporated under reduced pressure, and the precipitated crystals were washed with ether to give 3.98 g of 11-(2-aminoethyl)amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

(6) To a solution of 0.62 g (0.8 mmol) of the compound obtained in the above (5) in 10 ml of a mixture of methylene chloride and pyridine was added 0.22 g (1.0

mmol) of quinoline-8-sulfonyl chloride under ice-cooling, followed by stirring at room temperature for 2 hours. After the reaction, the reaction solution was diluted with ethyl acetate and washed with an aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and purification by silica gel column chromatography (chloroform : methanol : aqueous ammonia =20:1:0.1) gave 0.62 g (yield: 80 %) of the title compound.

IonSprayMS m/z: 968.5 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.81 (s, 3H, 6-OMe), 3.93 and 3.97 (each d, each 1H, $J_{gem}$=16.2 Hz, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 5.04 (d, 1H, J=11.0 Hz, H-3), 5.11 (dd, 1H, J=11.0, 2.4 Hz, H-13), 6.79 (brt, 1H, J=6.4 Hz, -$NHSO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 49.9 (6-OMe), 103.6 (C1'), 157.5 (11,12-carbamate), 170.4 (-$COCH_2$[2-Pyridine]), 174.1 (C1), 215.7 (C9).

Example 11

11-[2-[(3-Nitrophenyl)sulfonylaminolethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.68 mmol) of the compound obtained

in Example 10(5) and 0.18 g (0.23 mmol) of 3-nitrobenzenesulfonyl chloride, there was obtained 0.55 g (yield: 85 %) of the title compound.

SIMS m/z: 962 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.87 (s, 3H, 6-OMe), 3.93 and 3.96 (each d, each 1H, $J_{gem}$=16.2 Hz, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 4.92 (dd, 1H, J=11.0, 2.4Hz, H-13), 4.99 (d, 1H, J=11.0 Hz, H-3), 6.31 (brs, 1H, -$NHSO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.1 (6-OMe), 103.5 (C1'), 157.7 (11,12-carbamate), 170.4 (-$COCH_2$[2-Pyridine]), 175.5 (C1), 216.0 (C9).

Example 12

11-[2-[(3-Nitrophenyl)sulfonylamino]ethyl]-amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedure as in Example 1 for oxidation using 72.0 g of the compound obtained in Example 10(2), there was obtained 67.0 g of 2'-O-acetyl-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate.

(2) Following the same procedure as in Example 10(2) using 67.0 g of the compound obtained in the above (1), there was obtained 19.8 g of the 10,11-anhydro compound.

(3) Following the same procedure as in Example 10(4) using 19.8 g of the compound obtained in the above

(2), purification by silica gel column chromatography (acetone : n-hexane : triethylamine =10:20:0.2) gave 15.5 g (yield: 68 %) of the 12-O-imidazolylcarbonyl compound.

(4) To a solution of 8.4 g (12 mmol) of the compound obtained in the above (3) in 60 ml of acetonitrile was added 8.0 ml (0.12 mol) of ethylenediamine, followed by stirring at room temperature for 2 days. After the reaction, the reaction solution was diluted with ethyl acetate and washed with distilled water and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure to give 7.1 g of 2'-O-acetyl-11-(2-aminoethyl)-amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methyl-erythronolide A 11,12-cyclic carbamate.

(5) To a solution of 0.52 g (0.75 mmol) of the compound obtained in the above (4) in 10 ml of a mixture of methylene chloride and pyridine was added 0.20 g (0.9 mmol) of 3-nitrobenzenesulfonyl chloride under ice-cooling, followed by stirring at room temperature overnight. After the reaction, the reaction solution was diluted with ethyl acetate and washed with an aqueous sodium hydroxide solution and a saturated aqueous sodium chloride solution successively. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in 20 ml of methanol, followed

by stirring at room temperature overnight. After the reaction, the solvent was evaporated under reduced pressure, and purification by silica gel column chromatography (chloroform : methanol : aqueous ammonia =27:1:0.1) gave 0.26 g (yield: 41 %) of the title compound.

SIMS m/z: 841 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.49 (s, 3H, 6-OMe), 3.83 (q, J=7.0 Hz, H-2), 4.21 (d, 1H, J=8.8 Hz, H-5), 4.26 (d, 1H, J=7.3 Hz, H-1'), 4.82 (dd, 1H, J=10.9, 2.4 Hz, H-13), 6.12 (brs, 1H, $-N\underline{H}SO_2-$)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 50.0 (6-OMe), 104.0 (C1'), 158.0 (11,12-carbamate), 170.4 (C1), 203.1 (C3), 216.6 (C9).

Example 13

11-[2-[(4-Nitrophenyl)sulfonylamino]ethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.51 g (0.66 mmol) of the compound obtained in Example 10(5) and 0.17 g (0.77 mmol) of 4-nitrobenzenesulfonyl chloride, there was obtained 0.51 g (yield: 80 %) of the title compound.

SIMS m/z: 962 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.89 (s, 3H, 6-OMe), 3.93 and 3.96 (each d, each 1H,

$J_{gem}$=16.5Hz, -C$\underline{H}_2$[2-Pyridine]), 4.06(d, 1H, J=7.3 Hz, H-1'), 4.91 (dd, 1H, J=11.0, 1.8 Hz, H-13), 5.00 (d, 1H, J=11.0 Hz, H-3), 6.32 (brs, 1H, -N$\underline{H}$SO$_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 50.1 (6-OMe), 103.5 (C1'), 157.9 (11,12-carbamate), 170.4 (-$\underline{C}$OCH$_2$[2-Pyridine]), 175.3 (C1), 216.1 (C9).

Example 14

<u>11-[2-[(4-Nitrophenyl)sulfonylamino]ethyl]-amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 12(5) using 0.83 g (1.2 mmol) of the compound obtained in Example 12(4) and 0.35 g (1.6 mmol) of 4-nitrobenzenesulfonyl chloride, there was obtained 0.41 g (yield: 41 %) of the title compound.

SIMS m/z: 841 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.51 (s, 3H, 6-OMe), 3.83 (q, J=6.7 Hz, H-2), 4.22 (d, 1H, J=9.2 Hz, H-5), 4.27 (d, 1H, J=7.3 Hz, H-1'), 4.82 (dd, 1H, J=11.0, 2.4 Hz, H-13), 6.14 (brs, 1H, -N$\underline{H}$SO$_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 49.7 (6-OMe), 104.0 (C1'), 158.2 (11,12-carbamate), 170.3 (C1), 203.2 (C3), 216.7 (C9).

Example 15

<u>11-[2-(Pentafluorophenylsulfonylamino)-</u>

ethyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.68 mmol) of the compound obtained in Example 10(5) and 0.22 g (0.83 mmol) of pentafluorobenzenesulfonyl chloride, there was obtained 0.29 g (yield: 42 %) of the title compound.

SIMS m/z: 1007 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 3.04 (s, 3H, 6-OMe), 3.78 (d, 1H, J=4.3 Hz, H-5), 3.92 and 3.96 (each d, each 1H, $J_{gem}$=15.9 Hz, -$CH_2$[2-Pyridine]), 4.07 (d, 1H, J=7.3 Hz, H-1'), 4.99 (dd, 1H, J=11.0, 2.4 Hz, H-13), 5.03 (d, 1H, J=11.0 Hz, H-3)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.4 (6-OMe), 103.5 (C1'), 157.7 (11,12-carbamate), 170.5 (-$C$O$CH_2$[2-Pyridine]), 175.5 (C1), 216.0 (C9).

Example 16

11-[2-(Pentafluorophenylsulfonylamino)-ethyllamino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 12(5) using 0.83 g (1.2 mmol) of the compound obtained in Example 12(4) and 0.38 g (1.4 mmol) of pentafluorobenzenesulfonyl chloride, there was obtained 0.49 g (yield: 46 %) of the title compound.

SIMS m/z: 886 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.26 (s, 6H, $NMe_2$), 2.62 (s, 3H, 6-OMe), 3.86 (q, J=6.7 Hz, H-2), 4.25 (d, 1H, J=9.2 Hz, H-5), 4.27 (d, 1H, J=7.3 Hz, H-1'), 4.90 (dd, 1H, J=11.0, 2.4 Hz, H-13)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2($NMe_2$), 49.9 (6-OMe), 104.0 (C1'), 157.7 (11,12-carbamate), 170.7 (C1), 203.0 (C3), 216.5 (C9).

Example 17

11-[2-(Methanesulfonylamino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.51 g (0.66 mmol) of the compound obtained in Example 10(5) and 0.06 ml (0.79 mmol) of methanesulfonyl chloride, there was obtained 0.45 g (yield: 80 %) of the title compound.

SIMS m/z: 855 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.98 (s, 3H, $-SO_2Me$), 3.05 (s, 3H, 6-OMe), 3.92 and 3.96 (each d, each 1H, $J_{gem}$=15.9 Hz, $-C\underline{H}_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3Hz, H-1'), 5.03 (d, 2H, J=10.9 Hz, H-3 and H-13), 5.51 (brt, 1H, J=5.5 Hz, $-N\underline{H}SO_2-$)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 41.2 ($-SO_2Me$), 50.3 (6-OMe), 103.5 (C1'), 157.9 (11,12-carbamate), 170.4 ($-\underline{C}OCH_2$[2-Pyridine]), 175.1 (C1), 216.0 (C9).

Example 18

11-[2-(methanesulfonylamino)ethyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 12(5) using 0.83 g (1.2 mmol) of the compound obtained in Example 12(4) and 0.11 ml (1.4 mmol) of methanesulfonyl chloride, there was obtained 0.18 g (yield: 21 %) of the title compound.

FABMS m/z: 734 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.27 (s, 6H, $NMe_2$), 2.66 (s, 3H, 6-OMe), 2.99 (s, 3H, $-SO_2Me$), 3.86 (q, J=6.7 Hz, H-2), 4.25 (d, 1H, J=9.2 Hz, H-5), 4.28 (d, 1H, J=7.3 Hz, H-1'), 4.95 (dd, 1H, J=11.0, 2.4 Hz, H-13), 5.33 (brs, 1H, $-NHSO_2-$)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 41.0 ($-SO_2Me$), 49.9 (6-OMe), 104.0 (C1'), 157.9 (11,12-carbamate), 170.3 (C1), 203.3 (C3), 216.5 (C9).

Example 19

11-[2-(Phenylsulfonylamino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.54 g (0.69 mmol) of the compound obtained in Example 10(5) and 0.15 g (0.85 mmol) of benzenesulfonyl chloride, there was obtained 0.52 g (yield: 82 %) of the title compound.

IonSpray MS m/z: 917.4 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.28 (s, 6H, $NMe_2$), 2.80 (s, 3H, 6-OMe), 3.92 and 3.96 (each d, each 1H, $J_{gem}$=15.8 Hz, -$CH_2$[2-Pyridine]), 4.05 (d, 1H, J=7.3 Hz, H-1'), 4.95 (dd, 1H, J=11.0, 2.2 Hz, H-13), 4.99 (d, 1H, J=11.0 Hz, H-3), 5.93 (brt, 1H, J=5.8 Hz, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.1 (6-OMe), 103.5 (C1'), 157.7 (11,12-carbamate), 170.4 (-<u>C</u>$OCH_2$[2-Pyridine]), 175.1 (C1), 215.9 (C9).

Example 20

<u>11-[2-(1-Naphthalenesulfonylamino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 10(6) using 0.54 g (0.69 mmol) of the compound obtained in Example 10(5) and 0.19 g (0.84 mmol) of naphthalenesulfonyl chloride, there was obtained 0.58 g (yield: 87 %) of the title compound.

IonSpray MS m/z: 967.4 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.28 (s, 6H, $NMe_2$), 2.67 (s, 3H, 6-OMe), 3.93 and 3.97 (each d, each 1H, $J_{gem}$=16.2 Hz, -$CH_2$[2-Pyridine]), 4.04 (d, 1H, J=7.3 Hz, H-1'), 5.02(dd, 1H, J=11.2, 2.2 Hz, H-13), 5.00 (d, 1H, J=11.0 Hz, H-3), 6.31(brt, 1H, J=5.8 Hz, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.0

(6-OMe), 103.6 (C1'), 157.7 (11,12-carbamate), 170.4 (-COCH$_2$[2-Pyridine]), 175.1 (C1), 215.8 (C9).

Example 21

11-[2-(2-Mesitylenesulfonylamino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.68 mmol) of the compound obtained in Example 10(5) and 0.18 g (0.82 mmol) of 2-mesitylenesulfonyl chloride, there was obtained 0.55 g (yield: 84 %) of the title compound.

IonSpray MS m/z: 959.5 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.27 and 2.63 (each s, 9H, -Ph$\underline{Me}_3$), 2.29 (s, 6H, $NMe_2$), 2.93(s, 3H, 6-OMe), 3.92 and 3.95 (each d, each 1H, $J_{gem}$=16.2 Hz, -C$\underline{H}_2$[2-Pyridine]), 4.05 (d, 1H, J=7.3 Hz, H-1'), 5.00-5.03 (m, 2H, H-3 and H-13), 5.92 (brt, 1H, J=6.0 Hz, -N$\underline{H}$SO$_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 20.8 and 22.9 (-Ph$\underline{Me}_3$), 40.3 ($NMe_2$), 50.2 (6-OMe), 103.5 (C1'), 157.8 (11, 12-carbamate), 170.4 (-$\underline{C}$OCH$_2$[2-Pyridine]), 174.8 (C1), 215.8 (C9).

Example 22

11-[2-[2-(1-Naphthyl)ethanesulfonylamino]-ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic

carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.68 mmol) of the compound obtained in Example 10(5) and 0.21 g (0.82 mmol) of 2-(1-naphthyl)ethanesulfonyl chloride, there was obtained 0.38 g (yield: 56 %) of the title compound.

IonSpray MS m/z: 995.5 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.31 (s, 6H, $NMe_2$), 3.04(s, 3H, 6-OMe), 3.91 and 3.96 (each d, each 1H, $J_{gem}$=15.9 Hz, -C$\underline{H}_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 5.03 (d, 1H, J=11.0 Hz, H-3), 5.04 (dd, 1H, J=11.0, 2.2 Hz, H-13), 5.60 (brs, 1H, -N$\underline{H}$SO$_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.3 (6-OMe), 103.5 (C1'), 158.0 (11,12-carbamate), 170.4 (-$\underline{C}$OCH$_2$[2-Pyridine]), 175.0 (C1), 216.0 (C9).

Example 23

11-[2-(2-Acetamido-4-methyl-5-thiazolesulfonyl-amino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.57 g (0.73 mmol) of the compound obtained in Example 10(5) and 0.22 g (0.86 mmol) of 2-acetamido-4-methyl-5-thiazolesulfonyl chloride, recrystallization from ethyl acetate/n-hexane gave 0.19 g (yield: 26 %) of the title compound as the first crystals.

FABMS m/z: 995 $[M+H]^+$

$^1$H-NMR (500MHz, $CDCl_3$) $\delta$ (ppm); 2.21 (s, 3H, -NHCOC<u>H</u>$_3$), 2.29 (s, 6H, $NMe_2$), 2.49 (s, 3H, [Thiazole]-Me), 2.91 (s, 3H, 6-OMe), 3.91 and 3.95 (each d, each 1H, $J_{gem}$=15.8 Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.05 (d, 1H, J=7.4 Hz, H-1'), 4.97 (d, 2H, J=11.3 Hz, H-3 and H-13), 6.08 (brs, 1H, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 16.3 ([Thiazole]-Me), 23.0 (-NHCO<u>C</u>H$_3$), 40.3 ($NMe_2$), 50.2 (6-OMe), 103.6 (C1'), 157.8 (11,12-carbamate), 168.1 (-NH<u>C</u>OCH$_3$), 170.5 (-<u>C</u>O$CH_2$[2-Pyridine]), 175.1 (C1), 215.9 (C9).

Example 24

<u>11-[2-[3,5-Dimethylisoxazole-4-sulfonyl-aminolethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 10(6) using 0.54 g (0.69 mmol) of the compound obtained in Example 10(5) and 0.16 g (0.82 mmol) of 3,5-dimethylisoxazole-4-sulfonyl chloride, there was obtained 0.28 g (yield: 44 %) of the title compound.

FABMS m/z: 936 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.41 and 2.64 (each s, each 3H, [Isoxazole]-Me), 2.96 (s, 3H, 6-OMe), 3.92 and 3.96 (each d, each 1H, $J_{gem}$=16.2 Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 4.95 (dd, 1H, J=11.0, 2.1 Hz, H-13), 5.02 (d, 1H, J=11.0 Hz, H-3), 6.31 (brs, 1H, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 10.7 and 12.6 ([Isoxazole]-Me), 40.3 ($NMe_2$), 50.1 (6-OMe), 103.6 (C1'), 158.1 (11,12-carbamate), 170.5 (-$\underline{C}OCH_2$[2-Pyridine]), 175.2 (C1), 216.1 (C9).

Example 25

11-[2-[2-(Pyrid-2-yl)thiophene-5-sulfonylaminolethyl]amino-11-deoxy-3-O-(2-pyridyl)-acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.69 mmol) of the compound obtained in Example 10(5) and 0.21 g (0.81 mmol) of 2-(pyrid-2-yl)thiophene-5-sulfonyl chloride, there was obtained 0.47 g (yield: 68 %) of the title compound.

FABMS m/z: 1000 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.94 (s, 3H, 6-OMe), 3.92 and 3.96 (each d, each 1H, $J_{gem}$=15.9 Hz, -$CH_2$[2-Pyridine]), 4.05 (d, 1H, J=7.3 Hz, H-1'), 5.01 (dd, 1H, J=11.0, 2.4 Hz, H-13), 5.02 (d, 1H, J=11.0 Hz, H-3), 6.14 (brs, 1H, -$NHSO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.2 (6-OMe), 103.5 (C1'), 157.8 (11,12-carbamate), 170.4 (-$\underline{C}OCH_2$[2-Pyridine]), 175.0 (C1), 215.9 (C9).

Example 26

11-[2-[(3-Pyridyl)sulfonylaminolethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methyl-

erythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 1.0 g (1.3 mmol) of the compound obtained in Example 10(5) and 0.69 g of pyridine-3-sulfonyl chloride described in the following Reference Example 2, there was obtained 0.20 g (yield: 17 %) of the title compound.

IonSprayMS m/z: 918.4 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.86 (s, 3H, 6-OMe), 3.93 and 3.96 (each d, each 1H, $J_{gem}$=15.9 Hz, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 4.93 (dd, 1H, J=11.0, 2.4 Hz, H-13), 5.00 (d, 1H, J=11.0 Hz, H-3), 6.21 (brs, 1H, -$NHSO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.1 (6-OMe), 103.5 (C1'), 157.8 (11,12-carbamate), 170.4 (-$COCH_2$[2-Pyridine]), 175.3 (C1), 216.0 (C9).

Reference Example 2

Preparation of pyridine-3-sulfonyl chloride

1.6 g (0.01 mol) of pyridine-3-sulfonic acid and 4.2 g (0.02 mol) of phosphorus pentachloride together were stirred at 200°C for 2.5 hours. After the reaction, chloroform was added to the reaction system, the insoluble matter was removed by filtration, and the filtrate was evaporated under reduced pressure to give 2.41 g of pyridine-3-sulfonyl chloride.

Example 27

11-[2-[(4-Methylphenyl)sulfonylaminolethyl]-

amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.69 mmol) of the compound obtained in Example 10(5) and 0.15 g (0.80 mmol) of p-toluenesulfonyl chloride, there was obtained 0.40 g (yield: 63 %) of the title compound.

IonSprayMS m/z: 931.5 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.39 (s, 3H, Ph-Me), 2.83 (s, 3H, 6-OMe), 3.93 and 3.96 (each d, each 1H, $J_{gem}$=15.9 Hz, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 4.96 (dd, 1H, J=11.0, 2.4 Hz, H-13), 5.00 (d, 1H, J=11.0 Hz, H-3), 5.83 (brt, 1H, J=6.1 Hz, -$NHSO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 21.4 (Ph-Me), 40.3 ($NMe_2$), 50.0 (6-OMe), 103.5 (C1'), 157.7 (11,12-carbamate), 170.4 (-$COCH_2$[2-Pyridine]), 175.0 (C1), 215.9 (C9).

Example 28

11-[2-[4-(4-Dimethylaminophenylazo)phenylsulfonylamino]ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.52 g (0.67 mmol) of the compound obtained in Example 10(5) and 0.26 g (0.80 mmol) of 4-(4-dimethylaminophenylazo)benzenesulfonyl chloride, there

was obtained 0.54 g (yield: 76 %) of the title compound.

IonSprayMS m/z: 1064.6 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.93 (s, 3H, 6-OMe), 3.11 (s, 6H, Ph-$NMe_2$), 3.92 and 3.96 (each d, each 1H, J=15.9 Hz, -$CH_2$[2-Pyridine]), 4.05 (d, 1H, J=7.3 Hz, H-1'), 4.98 (dd, J=11.0, 1.8 Hz, H-13), 5.04 (d, 1H, J=11.0 Hz, H-3), 6.03 (brt, 1H, J=6.1 Hz, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.2 ($NMe_2$), 40.3 ($NMe_2$), 50.2 (6-OMe), 103.5 (C1'), 157.9 (11,12-carbamate), 170.3 (-<u>C</u>O$CH_2$[2-Pyridine]), 174.9 (C1), 215.9 (C9).

Example 29

<u>11-[2-[(4-Methoxyphenyl)sulfonylamino]ethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 10(6) using 0.57 g (0.74 mmol) of the compound obtained in Example 10(5) and 0.18 g (0.87 mmol) of 4-methoxy-benzenesulfonyl chloride, there was obtained 0.45 g (yield: 64 %) of the title compound.

FABMS m/z: 947 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.83 (s, 3H, 6-OMe), 3.83 (s, 3H, Ph-OMe), 3.92 and 3.96 (each d, each 1H, J=15.9 Hz, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 4.96 (dd, 1H, J=11.0, 1.8 Hz, H-13), 5.01 (d, 1H, J=11.0 Hz, H-3), 5.79 (brt, 1H, J=6.1 Hz, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ (ppm); 40.3 ($NMe_2$), 50.1 (6-OMe), 55.5 (Ph-OMe), 103.5 (C1'), 157.7 (11,12-carbamate), 170.4 (-$\underline{C}OCH_2$[2-Pyridine]), 175.0 (C1), 215.8 (C9).

Example 30

11-[2-[(4-Cyanophenyl)sulfonylaminolethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.54 g (0.69 mmol) of the compound obtained in Example 10(5) and 0.17 g (0.84 mmol) of 4-cyano-benzenesulfonyl chloride, there was obtained 0.48 g (yield: 74 %) of the title compound.

FABMS m/z: 942 $[M+H]^+$

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.86 (s, 3H, 6-OMe), 3.95 (s, 2H, -$\underline{CH_2}$[2-Pyridine]), 4.07(d, 1H, J=7.3 Hz, H-1'), 4.91 (dd, 1H, J=11.0, 2.1 Hz, H-13), 5.01 (d, 1H, J=11.2 Hz, H-3).

Example 31

11-[2-[(4-Trifluoromethoxyphenyl)sulfonyl-aminolethyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.65 g (0.84 mmol) of the compound obtained in Example 10(5) and 0.26 g (1.0 mmol) of 4-(trifluoro-

methoxy)benzenesulfonyl chloride, there was obtained 0.36 g (yield: 43 %) of the title compound.

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.84 (s, 3H, 6-OMe), 3.94 (s, 2H, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.1 Hz, H-1'), 4.93 (dd, 1H, J=11.0, 1.9 Hz, H-13), 5.01 (d, 1H, J=10.8 Hz, H-3).

Example 32

11-[2-[(4-Trifluoromethylphenyl)sulfonyl-aminolethyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.52 g (0.67 mmol) of the compound obtained in Example 10(5) and 0.20 g (0.82 mmol) of 4-(trifluoromethyl)benzenesulfonyl chloride, there was obtained 0.45 g (yield: 68 %) of the title compound.

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm); 2.29 (s, 6H, $NMe_2$), 2.85 (s, 3H, 6-OMe), 3.94 (s, 2H, -$CH_2$[2-Pyridine]), 4.06 (d, 1H, J=7.3 Hz, H-1'), 4.91 (dd, 1H, J=11.0, 2.1 Hz, H-13), 5.01 (d, 1H, J=11.2 Hz, H-3).

Example 33

11-[2-(N-Phenylsulfamoyl)ethyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

To a solution of 0.15 g (0.17 mmol) of the compound obtained in Example 10(4) in 10 ml of a mixture

of N,N-dimethylformamide and distilled water [10:3] was added 0.34 g (1.7 mmol) of 2-aminoethylsulfonanilide described in the following Reference Example 3 at room temperature, followed by stirring for 7 days. After the reaction, chloroform was added to the reaction solution, and the mixture was successively washed with distilled water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in 10 ml of methanol and stirred at room temperature overnight. After the reaction, the solvent was evaporated under reduced pressure, and purification by silica gel column chromatography (chloroform : methanol : aqueous ammonia =19:1:0.1 - 9:1:0.1) gave 0.05 g (yield: 32 %) of the title compound.

FABMS m/z: 917 $[M+H]^+$

$^1$H-NMR (500MHz, $CDCl_3$) $\delta$ (ppm); 0.84 (t, 3H, J=7.3 Hz, 14-Me), 2.29 (s, 6H, $NMe_2$), 2.95 (s, 3H, 6-OMe), 5.06 (d, 1H, J=11.0 Hz, H-3), 5.48 (dd, 1H, J=11.0, 1.8 Hz, H-13).

Reference Example 3

Preparation of 2-aminoethylsulfonanilide

(1) To a solution of 8.0 g (64 mmol) of 2-aminoethylsulfonic acid (taurine) in 35 ml of distilled water were added 11.2 g (0.13 mol) of sodium bicarbonate and 19.8 g (0.12 mol) of carbobenzoxychloride under ice-

cooling, followed by stirring at room temperature for 4 hours. After the reaction, the reaction solution was washed with ether, the aqueous layer was made acidic with an aqueous hydrochloric acid solution, and the solution was concentrated under reduced pressure. The solution was allowed to stand overnight, and the precipitated crystals were recrystallized from water/methanol (1:10) to give 15.5 g (yield: 86 %) of carbobenzoxytaurine.

(2) To a suspension of 15.0 g (53.3 mmol) of the compound obtained in the above (1) in 150 ml of benzene was added 15.0 g (72 mmol) of phosphorus pentachloride, followed by refluxing under heating for 25 minutes. After the reaction, the reaction solution was evaporated under reduced pressure, and 150 ml of benzene was added thereto, followed by removal of the insoluble matter by filtration. The filtrate was evaporated under reduced pressure to give 15.0 g of sulfonyl chloride.

(3) To a solution of 3.7 g (13.2 mmol) of the compound obtained in the above (2) in 100 ml of methylene chloride were added 1.8 ml (19.0 mmol) of aniline, 4.0 ml (51.6 mmol) of pyridine and 0.16 g (1.3 mmol) of 4-dimethylaminopyridine, followed by stirring overnight. After the reaction, the reaction solution was washed with 1N aqueous hydrochloric acid solution, the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced

pressure. The residue was dissolved in 100 ml of methanol, and 0.5 g of palladium carbon was added thereto, followed by stirring under a hydrogen stream overnight. After the reaction, the catalyst in the reaction solution was removed by filtration, and the filtrate was concentrated under reduced pressure to give 1.7 g of 2-aminoethylsulfonanilide.

Example 34

11-[2-(N-Phenylsulfamoyl)ethyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 33 using 0.38 g (0.50 mmol) of the compound obtained in Example 12(3), 1.0 g (5.0 mmol) of 2-aminoethyl-sulfonanilide described in Reference Example 3, there was obtained 0.34 g (yield: 85 %) of the title compound.

FABMS m/z: 796 $[M+H]^+$

$^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ (ppm); 0.87 (t, 3H, J=7.3 Hz, 14-Me), 2.26 (s, 6H, $NMe_2$), 2.60 (s, 3H, 6-OMe), 4.23 (d, 1H, J=8.5 Hz, H-5).

Example 35

11-[2-[N-(4-Methoxyphenyl)sulfamoyl]ethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 33 using 0.50 g (0.57 mmol) of the compound obtained in

Example 10(4), 4-methoxyaniline in place of aniline and 1.30 g (5.7 mmol) of 4'-methoxy-2-aminoethyl-sulfonanilide prepared in the same manner as in Reference Example 3, there was obtained 0.06 g (yield: 11 %) of the title compound.

FABMS m/z: 947 $[M+H]^+$

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm); 0.83 (t, 3H, J=7.3 Hz, 14-Me), 2.29 (s, 6H, $NMe_2$), 2.97 (s, 3H, 6-OMe), 3.79 (s, 3H, Ph-OMe), 5.06 (d, 1H, J=10.6 Hz, H-3), 5.48 (dd, 1H, J=11.0, 2.0 Hz, H-13), 6.87 (m, 2H), 7.29 (m, 2H).

Example 36

11-[2-[N-(3-Pyridyl)sulfamoyl]ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 33 using 0.35 g (0.40 mmol) of the compound obtained in Example 10(4), 3-aminopyridine in place of aniline and 0.80 g (3.98 mmol) of 3-(2-aminoethyl)sulfonamidopyridine prepared in the same manner as in Reference Example 3, there was obtained 0.05 g (yield: 14 %) of the title compound.

FABMS m/z: 918 $[M+H]^+$

$^1$H-NMR (300 MHz, $CDCl_3$) $\delta$ (ppm); 0.84 (t, 3H, J=7.3 Hz, 14-Me), 2.29 (s, 6H, $NMe_2$), 2.99 (s, 3H, 6-OMe), 5.06 (d, 1H, J=11.0 Hz, H-3), 5.48 (dd, 1H, J=11.2, 2.0 Hz, H-13), 6.87 (m, 2H), 7.29 (m, 2H).

Example 37

11-[2-[(4-Nitrophenylsulfonyl)amino]ethyl]-amino-11-deoxy-3-O-methylthiomethyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedures as in Example 1(1) and (2) using 5.06 g (7.69 mmol) of the compound obtained in Reference Example 1 and 2.3 g (10.4 mmol) of 4-nitrobenzenesulfonyl chloride, there was obtained 7.31 g of the 2'-O-acetyl compound.

(2) Following the same procedure as in Example 2 using 4.02 g (4.54 mmol) of the compound obtained in the above (1), there were obtained 1.33 g (yield: 35 %) of the same compound as obtained in Example 14 and 0.15 g (yield: 4 %) of the title compound.

IonSpray MS m/z: 903.4[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.28(s, 6H, $NMe_2$), 2.29(s, 3H, SMe), 2.94(s, 3H, 6-OMe), 4.44(d, 1H, J=7.3Hz, H-1'), 4.68 and 4.92(each d, each 1H, J=11.0Hz, -OC$\underline{H}_2$SMe), 4.86(dd, 1H, J=11.0, 1.8Hz, H-13)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm)15.8(SMe), 40.2($NMe_2$), 50.2(6-OMe), 77.7(-O$\underline{C}H_2$SMe), 101.7(C1'), 158.0(11, 12-carbamate), 176.5(C1), 216.2(C9).

Example 38

11-[2-(3-Pyridylsulfonylamino)ethyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methyl-erythronolide A 11,12-cyclic carbamate

(1) Following the same procedures as in

Example 1(1) and (2) using 1.00 g (1.52 mmol) of the compound obtained in Reference Example 1 and 0.60 g (3.4 mmol) of 3-pyridylsulfonyl chloride obtained in Reference Example 2, there was obtained 0.42 g of the 2'-O-acetyl compound.

(2) Following the same procedure as in Example 2 using 0.42 g (0.5 mmol) of the compound obtained in the above (1), there was obtained 0.21 g (yield: 17 %) of the title compound.

IonSpray MS m/z: 797.4[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.26(s, 6H, $NMe_2$), 2.51(s, 3H, 6-OMe), 3.84(q, 1H, J=6.7Hz, H-2), 4.22(d, 1H, J=9.2Hz, H-5), 4.27(d, 1H, J=7.3Hz, H-1'), 4.86(dd, 1H, J=11.0, 2.4Hz, H-13), 6.12(brs, 1H, -NHSO$_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm)40.2($NMe_2$), 49.7(6-OMe), 103.9(C1'), 158.0(11,12-carbamate), 170.2(C1), 203.2(C3), 216.6(C9).

Example 39

<u>11-[2-[(5-[2-(Methylthio)pyrimidin-4-yl]thiophene-2-sulfonylaminolethyl]amino-11-deoxy-3-O-(2-pyridyl)-acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 10(6) using 0.55 g (0.71 mmol) of the compound obtained in Example 10(5) and 0.26 g (0.85 mmol) of 5-[2-(methylthio)pyrimidin-4-yl]thiophene-2-sulfonyl chloride, there was obtained 0.50 g (yield: 67 %) of the title

compound.

FABMS m/z: 1047[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.30(s, 6H, $NMe_2$), 2.60(s, 3H, SMe), 2.91(s, 3H, 6-OMe), 3.92 and 3.96(each d, each 1H, J=15.9Hz, -$CH_2$[2-Pyridine]), 4.26(d, 1H, J=7.3Hz, H-1'), 4.98(dd, 1H, J=11.0, 1.8Hz, H-13), 5.00(d, 1H, J=11.6Hz, H-3), 6.24(brs, 1H, -N$H$$SO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)14.1(SMe), 40.3($NMe_2$), 50.1(6-OMe), 103.5(C1'), 157.6(11,12-carbamate), 170.4(-$C$$OCH_2$[2-Pyridine]), 175.2(C1), 216.0(C9).

Example 40

11-[2-(6-Chloroimidazo[2,1-b]thiazole-5-sulfonylamino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.62 g (0.80 mmol) of the compound obtained in Example 10(5) and 0.26 g (1.0 mmol) of 6-chloroimidazo[2,1-b]thiazole-5-sulfonyl chloride, there was obtained 0.16 g (yield: 19 %) of the title compound.

FABMS m/z:997[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.30(s, 6H, $NMe_2$), 2.85(s, 3H, 6-OMe), 3.92 and 3.96(each d, each 1H, J=15.9Hz, -$CH_2$[2-Pyridine]), 4.06(d, 1H, J=7.3Hz, H-1'), 4.99(d, 1H, J=11.0Hz, H-3), 5.00(dd, 1H, J=11.0, 2.4Hz, H-13), 6.65(brs, 1H, -N$H$$SO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.3($NMe_2$), 50.0(6-OMe),

103.5(C1'), 157.8(11,12-carbamate), 170.4(-COCH$_2$[2-Pyridine]), 175.3(C1), 215.9(C9).

Example 41

11-[2-(5-Chloro-3-methylbenzo[b]thiophene-2-sulfonylamino)ethyllamino-11-deoxy-3-O-(2-pyridyl)-acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.51 g (0.65 mmol) of the compound obtained in Example 10(5) and 0.22 g (0.78 mmol) of 5-chloro-3-methylbenzo[b]thiophene-2-sulfonyl chloride, there was obtained 0.45 g (yield: 67%) of the title compound.

FABMS m/z:1021$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.29(s, 6H, $NMe_2$), 2.66(s, 3H, benzothiophene-Me), 2.88(s, 3H, 6-OMe), 3.93 and 3.96(each d, each 1H, J=15.9Hz, -C$H_2$[2-Pyridine]), 4.05(d, 1H, J=6.7Hz, H-1'), 4.97-5.00(m, 1H, H-13), 5.01(d, 1H, J=11.6Hz, H-3), 6.48(brs, 1H, -NHSO$_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm)12.2(benzothiophene-Me), 40.3($NMe_2$), 50.1(6-OMe), 103.5(C1'), 157.9(11,12-carbamate), 170.4(-COCH$_2$[2-Pyridine]), 175.2(C1), 215.9(C9).

Example 42

11-[2-(4-Methylsulfonylbenzenesulfonylamino)-ethyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic

carbamate

Following the same procedure as in Example 10(6) using 0.53 g (0.68 mmol) of the compound obtained in Example 10(5) and 0.23 g (0.90 mmol) of 4-methylsulfonylbenzenesulfonyl chloride, there was obtained 0.36 g (yield: 53 %) of the title compound.

FABMS m/z:995$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.29(s, 6H, $NMe_2$), 2.87(s, 3H, 6-OMe), 3.08(s, 3H, $SO_2Me$), 3.93 and 3.96(each d, each 1H, J=15.9Hz, -$CH_2$[2-Pyridine]), 4.07(d, 1H, J=7.3Hz, H-1'), 4.92(dd, 1H, J=11.0, 1.8Hz, H-13), 5.00(d, 1H, J=11.0Hz, H-3), 6.30(brs, 1H, -$NHSO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm)40.3($NMe_2$), 44.2($SO_2Me$), 50.1(6-OMe), 103.5(C1'), 157.8(11,12-carbamate), 170.6(-$COCH_2$[2-Pyridine]), 175.5(C1), 216.0(C9).

Example 43

11-[2-(2-Thiophenesulfonylamino)ethylamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.52 g (0.66 mmol) of the compound obtained in Example 10(5) and 0.15 g (0.82 mmol) of 2-thiophenesulfonyl chloride, there was obtained 0.46 g (yield: 75 %) of the title compound.

FABMS m/z:923$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.29(s, 6H, $NMe_2$), 2.88(s, 3H, 6-OMe), 3.92 and 3.96(each d, each 1H, J=15.9Hz,

-C<u>H</u>$_2$[2-Pyridine]), 4.06(d, 1H, J=7.3Hz, H-1'), 4.98(dd, 1H, J=11.0, 1.8Hz, H-13), 5.01(d, 1H, J=11.0Hz, H-3), 6.10(brs, 1H, -N<u>H</u>SO$_2$-)

$^{13}$C-NMR(125MHz, CDCl$_3$) δ(ppm)40.3(NMe$_2$), 50.1(6-OMe), 103.5(C1'), 157.7(11,12-carbamate), 170.5(-<u>C</u>OCH$_2$[2-Pyridine]), 175.1(C1), 215.9(C9).

Example 44

<u>11-[2-[5-(Isoxazol-3-yl)thiophene-2-sulfonylaminolethyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 10(6) using 0.58 g (0.75 mmol) of the compound obtained in Example 10(5) and 0.22 g (0.88 mmol) of 5-(isoxazol-3-yl)thiophene-2-sulfonyl chloride, there was obtained 0.36 g (yield: 48 %) of the title compound.

FABMS m/z:990[M+H]$^+$

$^1$H-NMR(500MHz, CDCl$_3$) δ(ppm)2.29(s, 6H, NMe$_2$), 2.93(s, 3H, 6-OMe), 3.91 and 3.95(each d, each 1H, J=15.9Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.05(d, 1H, J=7.3Hz, H-1'), 4.95(dd, 1H, J=11.0, 2.2Hz, H-13), 5.01(d, 1H, J=10.9Hz, H-3), 6.30(brs, 1H, -N<u>H</u>SO$_2$-)

$^{13}$C-NMR(125MHz, CDCl$_3$) δ(ppm)40.3(NMe$_2$), 50.2(6-OMe), 103.5(C1'), 157.9(11,12-carbamate), 170.4(-<u>C</u>OCH$_2$[2-Pyridine]), 175.2(C1), 216.0(C9).

Example 45

11-[2-(Benzofurazan-4-sulfonylamino)ethyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.58 g (0.75 mmol) of the compound obtained in Example 10(5) and 0.19 g (0.87 mmol) of benzofurazan-4-sulfonyl chloride, there was obtained 0.47 g (yield: 66 %) of the title compound.

FABMS m/z:990[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.29(s, 6H, $NMe_2$), 3.02(s, 3H, 6-OMe), 3.93 and 3.96(each d, each 1H, J=15.9Hz, -$CH_2$[2-Pyridine]), 4.08(d, 1H, J=7.3Hz, H-1'), 5.02(dd, 1H, J=11.0Hz, H-3), 5.11(dd, 1H, J=11.0, 1.8Hz, H-13), 6.48(brs, 1H, -$NHSO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.3($NMe_2$), 50.5(6-OMe), 103.5(C1'), 157.1(11,12-carbamate), 170.4(-$COCH_2$[2-Pyridine]), 175.3(C1), 215.8(C9).

Example 46

11-[2-(2-Methylsulfonylbenzenesulfonylamino)-ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.52 g (0.67 mmol) of the compound obtained in Example 10(5) and 0.21 g (0.82 mmol) of 2-methylsulfonylbenzenesulfonyl chloride, there was

obtained 0.46 g (yield: 66 %) of the title compound.

FABMS m/z:995[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.29(s, 6H, $NMe_2$), 2.92(s, 3H, 6-OMe), 3.92 and 3.96(each d, each 1H, J=15.9Hz, $-CH_2$[2-Pyridine]), 3.39(s, 3H, $SO_2Me$), 4.05(d, 1H, J=7.3Hz, H-1'), 5.00(d, 1H, J=11.0Hz, H-3), 5.04(dd, 1H, J=11.0, 1.8Hz, H-13), 6.40(brt, 1H, J=5.5Hz, $-NHSO_2-$)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.3($NMe_2$), 50.1(6-OMe), 103.6(C1'), 157.2(11,12-carbamate), 170.4($-COCH_2$[2-Pyridine]), 174.0(C1), 215.6(C9).

Example 47

11-[2-(4-Nitrobenzenesulfonylamino)butyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedure as in Example 10(5) using 3.0 g (4.25 mmol) of the compound obtained in Example 12(3) and 4.3 ml (43 mmol) of 1,4-diaminobutane, there was obtained 3.2 g of 11-(3-aminobutyl)amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

(2) Following the same procedure as in Example 10(6) using 0.61 g (0.88 mmol) of the compound obtained in the above (1) and 0.26 g (1.2 mmol) of 4-nitrobenzenesulfonyl chloride, there was obtained 0.45 g (yield: 58 %) of the title compound.

FABMS m/z:869[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.27(s, 6H, $NMe_2$), 2.60(s, 3H, 6-OMe), 3.87(q, 1H, J=6.7Hz, H-2), 4.26(d, 1H, J=8.6Hz, H-5), 4.29(d, 1H, J=7.3Hz, H-1'), 4.88(dd, 1H, J=11.0, 1.8Hz, H-13), 5.65(brs, 1H, -NHSO$_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.2($NMe_2$), 49.9(6-OMe), 104.0(C1'), 157.3(11,12-carbamate), 170.1(C1), 203.4(C3), 216.9(C9).

Example 48

11-[2-(4-Nitrobenzenesulfonylamino)butyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedure as in Example 10(5) using 5.0 g (6.1 mmol) of the compound obtained in Example 10(4) and 6.1 ml (61 mmol) of 1,4-diaminopropane, there was obtained 4.9 g of 11-(3-aminobutyl)amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

(2) Following the same procedure as in Example 10(6) using 0.45 g (0.56 mmol) of the compound obtained in the above (1) and 0.14 g (0.63 mmol) of 4-nitrobenzenesulfonyl chloride, there was obtained 0.34 g (yield: 62 %) of the title compound.

FABMS m/z:990$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm) 2.30(s, 6H, $NMe_2$), 3.00(s, 3H, 6-OMe), 3.93 and 3.99(each d, each 1H, J=15.9Hz, -$CH_2$[2-Pyridine]), 4.08(d, 1H, J=7.3Hz, H-1'), 4.97(dd, 1H, J=11.0, 2.1Hz, H-13), 5.06(d, 1H,

J=11.2Hz, H-3).

Example 49

11-[2-(2-Acetamido-4-methyl-5-thiazolesulfonylamino)butyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.43 g (0.53 mmol) of the compound obtained in Example 48(1) and 0.16 g (0.63 mmol) of 2-acetamido-4-methyl-5-thiazolesulfonyl chloride, there was obtained 0.38 g (yield: 70 %) of the title compound.

FABMS m/z:1023 $[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm) 2.23(s, 3H, $COCH_3$), 2.29(s, 6H, $NMe_2$), 2.98(s, 3H, 6-OMe), 3.93 and 3.98(each d, each 1H, J=15.9Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.08(d, 1H, J=7.3Hz, H-1'), 4.98(dd, 1H, J=11.0, 2.1Hz, H-13), 5.02(d, 1H, J=11.3Hz, H-3), 5.63(brt, 1H, J=5.8Hz, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm) 22.9($COCH_3$), 40.3($NMe_2$), 50.2(6-OMe), 103.6(C1'), 157.5(11, 12-carbamate), 168.2($COCH_3$), 170.7(-<u>C</u>$OCH_2$[2-Pyridine]), 174.5(C1), 216.4(C9).

Example 50

11-[2-(3-Pyridylsulfonylamino)butyllamino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.58 g (0.72 mmol) of the compound obtained in Example 48(1) and 0.38 g (2.14 mmol) of 3-pyridylsulfonyl chloride obtained in Reference Example 2, there was obtained 0.51 g (yield: 75 %) of the title compound.

FABMS m/z:946$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm) 2.30(s, 6H, $NMe_2$), 3.04(s, 3H, 6-OMe), 3.93 and 3.97(each d, each 1H, J=15.9Hz, -$CH_2$[2-Pyridine]), 4.08(d, 1H, J=7.3Hz, H-1'), 4.98(dd, 1H, J=11.0, 1.8Hz, H-13), 5.06(d, 1H, J=11.0Hz, H-3), 5.77(brs, 1H, -$NHSO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm) 40.3($NMe_2$), 50.4(6-OMe), 103.6(C1'), 157.4(11, 12-carbamate), 170.4(-$COCH_2$[2-Pyridine]), 174.8(C1), 216.9(C9).

Example 51

11-[2-(3-Pyridylsulfonylamino)butyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.78 g (1.15 mmol) of the compound obtained in Example 47(1) and 0.61 g (3.43 mmol) of 3-pyridylsulfonyl chloride obtained in Reference Example 2, there was obtained 0.39 g (yield: 41 %) of the title compound.

FABMS m/z:825$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.27(s, 6H, $NMe_2$), 2.63(s,

3H, 6-OMe), 3.87(q, 1H, J=6.7Hz, H-2), 4.27(d, 1H, J=10.4Hz, H-5), 4.29(d, 1H, J=7.3Hz, H-1'), 4.90(dd, 1H, J=11.0, 1.8Hz, H-13), 5.68(brs, 1H, -NHSO$_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.2($NMe_2$), 50.0(6-OMe), 103.9(C1'), 157.3(11,12-carbamate), 170.1(C1), 203.4(C3), 216.9(C9).

Example 52

11-[2-(2-Dibenzofuransulfonylamino)ethyllamino-3,11-dideoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.33 g (0.42 mmol) of the compound obtained in Example 10(5) and 0.13 g (0.49 mmol) of 2-dibenzofuransulfonyl chloride, there was obtained 0.24 g (yield: 57 %) of the title compound.

FABMS m/z:1007$[M+H]^+$

$^1$H-NMR(300MHz, $CDCl_3$) δ(ppm)2.29(s, 6H, $NMe_2$), 2.88(s, 3H, 6-OMe), 3.97 and 3.91(each d, each 1H, J=15.9Hz, -CH$_2$[2-Pyridine]), 4.05(d, 1H, J=7.3Hz, H-1'), 4.96(dd, 1H, J=11.0, 2.0Hz, H-13), 5.01(d, 1H, J=11.2Hz, H-3), 6.00(brt, 1H, -NHSO$_2$-).

Example 53

11-[2-(2-Methylsulfonylbenzenesulfonylamino)-ethyllamino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example

12(5) using 0.51 g (0.73 mmol) of the compound obtained in Example 12(4) and 0.22 g (0.86 mmol) of 2-methylsulfonylbenzenesulfonyl chloride, there was obtained 0.46 g (yield: 72 %) of the title compound.

IonSprayMS m/z:874.2$[M+H]^+$

$^1$H-NMR(300MHz, $CDCl_3$) $\delta$(ppm)2.26(s, 6H, $NMe_2$), 2.55(s, 3H, 6-OMe), 3.40(s, 3H, $SO_2Me$), 4.96(dd, 1H, J=10.6, 2.5Hz, H-13), 6.37(brt, 1H, J=6.2Hz, -N<u>H</u>$SO_2$-)

Example 54

<u>11-[2-[2-(Pyrid-2-yl)thiophene-5-sulfonylaminolethyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 12(5) using 0.51 g (0.73 mmol) of the compound obtained in Example 12(4) and 0.24 g (0.92 mmol) of 2-(pyrid-2-yl)thiophene-5-sulfonyl chloride, there was obtained 0.33 g (yield: 48 %) of the title compound.

IonSprayMS m/z:879.3$[M+H]^+$

$^1$H-NMR(300MHz, $CDCl_3$) $\delta$(ppm)2.26(s, 6H, $NMe_2$), 2.58(s, 3H, 6-OMe), 4.22(d, 1H, J=8.7Hz, H-5), 4.27(d, 1H, J=7.3Hz, H-1'), 4.92(dd, 1H, J=10.6, 2.3Hz, H-13), 6.00(brs, 1H, -N<u>H</u>$SO_2$-).

Example 55

<u>11-[2-(2-Methylsulfonylbenzenesulfonylamino)-ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-</u>

desosaminylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedure as in Example 10(5) using 2.47 g of 2'-O-acetyl-10,11-anhydro-12-O-imidazolylcarbonyl-3-O-(2-pyridyl)acetyl-5-O-desosaminylerythronolide A, there was obtained 2.29 g of 11-(2-aminoethyl)amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminylerythronolide A 11,12-cyclic carbamate.

(2) Following the same procedure as in Example 10(6) using 0.52 g (0.68 mmol) of the compound obtained in the above (1) and 0.21 g (0.82 mmol) of 2-methylsulfonylbenzenesulfonyl chloride, there was obtained 0.38 g (yield: 57 %) of the title compound.

FABMS m/z:981$[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.33(s, 6H, $NMe_2$), 3.40(s, 3H, $SO_2Me$), 3.91 and 3.95(each d, each 1H, J=15.3Hz, -C<u>H</u>$_2$[2-Pyridine]), 4.57(d, 1H, J=7.3Hz, H-1'), 4.99 and 5.48(each brs, each 1H, H-3 and H-13), 6.25(brs, 1H, -N<u>H</u>$SO_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.5($NMe_2$), 44.3($SO_2Me$), 104.5(C1'), 156.5(11, 12-carbamate), 170.0(-<u>C</u>$OCH_2$[2-Pyridine]), 174.6(C1), 214.5(C9).

Example 56

11-[2-[(2-Acetamido-4-methyl-5-thiazolesulfonyl)aminoethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedure as in Example

10(5) using 5.0 g (6.1 mmol) of the compound obtained in Example 10(4) and 4.5 g (61 mmol) of 1,3-diaminopropane, there was obtained 4.5 g of 11-(3-aminopropyl)amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

(2) Following the same procedure as in Example 10(6) using 0.50 g (0.63 mmol) of the compound obtained in the above (1) and 0.24 g (0.95 mmol) of 2-acetamido-4-methyl-5-thiazolesulfonyl chloride, there was obtained 0.47 g (yield: 74 %) of the title compound.

FABMS m/z:1009 $[M+H]^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)0.76(t, 3H, J=7.3Hz, 14-Me), 2.29(s, 6H, $NMe_2$), 2.93(s, 3H, 6-OMe), 4.07(d, 1H, J=7.3Hz, H-1'), 4.92(dd, 1H, J=11.0, 2.1Hz, H-13), 5.01(d, 1H, J=11.0Hz, H-3).

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm)40.3($NMe_2$), 50.0(6-OMe), 103.7(C1'), 157.9(11,12-carbamate), 174.5(C1), 216.0(C9).

Example 57

<u>11-[3-(4-Nitrobenzenesulfonyl)aminopropyl]-amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate</u>

Following the same procedure as in Example 10(6) using 0.50 g (0.63 mmol) of the compound obtained in Example 56(1) and 0.21 g (0.95 mmol) of 4-nitrobenzenesulfonyl chloride, there was obtained 0.45 g (yield: 21 %) of the title compound.

FABMS m/z:976[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.29(s, 6H, $NMe_2$), 2.98(s, 3H, 6-OMe), 4.06(d, 1H, J=7.3Hz, H-1'), 4.83(dd, 1H, J=11.0, 1.8Hz, H-13), 5.02(d, 1H, J=11.0Hz, H-3).

$^{13}$C-NMR(125MHz, $CDCl_3$) δ(ppm)40.3($NMe_2$), 50.0(6-OMe), 103.6(C1'), 158.1(11,12-carbamate), 174.7(C1), 216.1(C9).

Example 58

11-[3-(3-Pyridylsulfonyl)aminopropyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.50 g (0.63 mmol) of the compound obtained in Example 56(1) and 0.40 g (2.3 mmol) of pyridine-3-sulfonyl chloride obtained in Reference Example 2, there was obtained 0.24 g (yield: 21 %) of the title compound.

FABMS m/z:932[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) δ(ppm)2.29(s, 6H, $NMe_2$), 2.99(s, 3H, 6-OMe), 4.06(d, 1H, J=7.3Hz, H-1'), 4.86(dd, 1H, J=11.0, 2.4Hz, H-13), 5.02(d, 1H, J=11.6Hz, H-3), 5.89(brs, 1H, -N<u>H</u>$SO_2$-).

Example 59

11-[3-[(2-Acetamido-4-methyl-5-thiazolesulfonyl)amino]propyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) Following the same procedure as in Example 10(5) using 2.0 g (2.8 mmol) of the compound obtained in Example 12(3) and 2.1 g (28 mmol) of 1,3-diaminopropane, there was obtained 2.0 g of 11-(3-aminopropyl)amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

(2) Following the same procedure as in Example 10(6) using 0.40 g (0.56 mmol) of the compound obtained in the above (1) and 0.22 g (0.84 mmol) of 2-acetamido-4-methyl-5-thiazolesulfonyl chloride, there was obtained 0.31 g (yield: 62 %) of the title compound.

FABMS m/z:888[M+H]$^+$

$^1$H-NMR(500MHz, $CDCl_3$) $\delta$(ppm)2.27(s, 6H, $NMe_2$), 2.62(s, 3H, 6-OMe), 4.23(d, 1H, J=9.2Hz, H-5), 4.28(d, 1H, J=7.3Hz, H-1'), 4.84(dd, J=11.0, 2.4Hz, H-13), 5.89(brs, 1H, -NHSO$_2$-)

$^{13}$C-NMR(125MHz, $CDCl_3$) $\delta$(ppm)40.2($NMe_2$), 49.9(6-OMe), 104.0(C1'), 158.0(11, 12-carbamate), 169.8(C1), 203.5(C3), 216.4(C9).

Example 60

11-[3-(3-Pyridylsulfonyl)aminopropyl]amino-3,11-dideoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.39 g (0.58 mmol) of the compound obtained in Example 59(1) and 0.22 g (0.84 mmol) of 2-acetamido-4-methyl-5-thiazolesulfonyl chloride, there was obtained

0.31 g (yield: 51 %) of the title compound.

FABMS m/z:811[M+H]$^+$

$^1$H-NMR(300MHz, $CDCl_3$) δ(ppm)0.76(t, 1H, J=7.5Hz, 14-Me), 2.27(s, 6H, $NMe_2$), 2.60(s, 3H, 6-OMe), 4.23(d, 1H, J=8.6Hz, H-5), 4.28(d, 1H, J=7.3Hz, H-1'), 4.78(dd, J=11.0, 2.4Hz, H-13), 5.82(brs, 1H, -NHSO$_2$-)

Example 61

11-[2-[N-(2-Methylsulfonylbenzene)sulfonyl-N-methylamino]ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

(1) 8.0 g (9.14 mmol) of 11-[2-(N-methyl-N-benzylamino)ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate was hydrogenated in methanol using palladium-carbon in an ordinary manner. The reaction solution was filtered, and the solvent was evaporated under reduced pressure to give 5.0 g (yield: 69 %) of the debenzylated compound.

(2) Following the same procedure as in Example 10(6) using 0.40 g (0.51 mmol) of the compound obtained in the above (1) and 0.16 g (0.61 mmol) of 2-methylsulfonylbenzenesulfonyl chloride, there was obtained 0.39 g (yield: 76 %) of the title compound.

SIMS m/z:1009[M+H]$^+$

$^1$H-NMR(300MHz, $CDCl_3$) δ(ppm)0.82(t, 3H, J=7.3Hz, 14-Me), 2.29(s, 6H, $NMe_2$), 2.99(s, 3H, 6-OMe), 4.06(d, 1H,

J=7.3Hz, H-1'), 5.03-5.11(m, 2H, H-3 and H-13).

Example 62

11-[2-[N-(6-Chloroimidazo[2,1,6]thiazole-5-sulfonyl)-N-methylamino]ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.40 g (0.51 mmol) of the compound obtained in Example 61 and 0.16 g (0.61 mmol) of 6-chloroimidazo-[2,1,6]thiazole-5-sulfonyl chloride, there was obtained 0.38 g (yield: 74 %) of the title compound.

SIMS m/z:1011$[M+H]^+$

$^1$H-NMR(300MHz, $CDCl_3$) $\delta$(ppm)0.81(t, 3H, J=7.3Hz, 14-Me), 2.30(s, 6H, $NMe_2$), 3.03(s, 3H, 6-OMe), 4.06(d, 1H, J=7.3Hz, H-1'), 5.03-5.11(m, 2H, H-3 and H-13).

Example 63

11-[2-[N-(3-Pyridylsulfonyl)-N-methylamino]-ethyl]amino-11-deoxy-3-O-(2-pyridyl)acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

Following the same procedure as in Example 10(6) using 0.40 g (0.51 mmol) of the compound obtained in Example 61 and 0.18 g (1.02 mmol) of pyridine-3-sulfonyl chloride, there was obtained 0.25 g (yield: 53 %) of the title compound.

SIMS m/z:932$[M+H]^+$

$^1$H-NMR(300MHz, $CDCl_3$) δ(ppm)0.83(t, 3H, J=7.3Hz, 14-Me), 2.30(s, 6H, $NMe_2$), 2.97(s, 3H, 6-OMe), 4.07(d, 1H, J=7.3Hz, H-1'), 5.04(dd, 1H, J=11.0, 2.3Hz, H-13), 5.05(d, 1H, J=11.2Hz, H-3).

Example 64

11-[2-[(2-Nitrophenyl)sulfonylaminolethyl]-amino-11-deoxy-3-O-[(3-pyridylmethyl)aminolcarbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

To a solution of 2.2 g (2.5 mmol) of the compound obtained in Example 3(1) in 10 ml of pyridine was added dropwise a solution of 0.74 g (2.5 mmol) of triphosgene in 10 ml of methylene chloride under ice-cooling, followed by stirring for 30 minutes. To the mixture was added 1.25 ml (12.3 mmol) of 3-(aminomethyl)pyridine, followed by stirring for 1.5 hours. After completion of the reaction, the same working-up and removal of the acetyl group at the 2'-position as in Example 1(3) gave 1.6 g of the title compound.

FABMS m/z: 977 $[M+H]^+$

Example 65

11-[2-[(2-Nitrophenyl)sulfonylaminol-ethyllamino-11-deoxy-3-O-(3-pyridyloxy)carbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

To a solution of 2.2 g (2.5 mmol) of the compound obtained in Example 3(1) in 10 ml of pyridine was added dropwise a solution of 0.74 g (2.5 mmol) of triphosgene in 10 ml of methylene chloride under ice-cooling, followed by stirring for 30 minutes. To the mixture was added 1.18 g (12.4 mmol) of 3-hydroxypyridine, followed by stirring for 1.5 hours. After completion of the reaction, the same working-up and removal of the acetyl group at the 2'-position as in Example 1(3) gave 1.2 g of the title compound.

FABMS m/z: 964 $[M+H]^+$

Test Example

The in vitro antibacterial activity of the compound obtained in Example 13 as an example of the compound of the present invention against various experimental bacteria was measured using sensitive disc media (produced by Eiken Chemical Co.) according to the MIC measuring method specified by the Japan Society of Chemotherapy. The results are expressed as MIC value (Minimum Inhibitory Concentration, μg/ml), and shown in Table 1.

[Table 1]

In Vitro Antibacterial Activity: MIC (μg/ml)

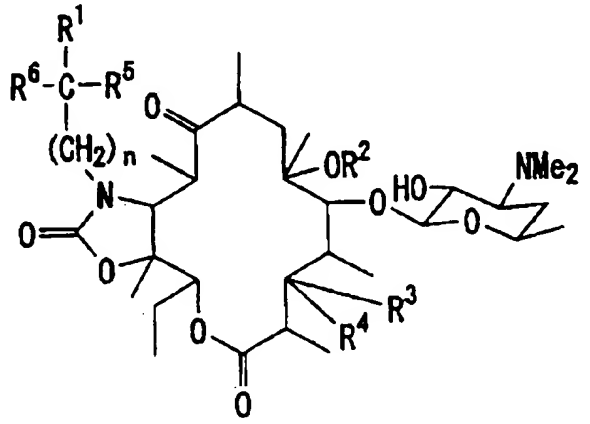
| Microorganism \ Compound | Compound of Example 13 |
|---|---|
| S. aureus 209P-JC | 0.10 |
| S. aureus Smith | 0.20 |
| S. epidermidis IID 866 | 0.025 |
| E. faecalis CSJ 1212 | 0.10 |
| S. pneumoniae BM 225 | 0.78 |
| S. pneumoniae BM 205 | 1.56 |

INDUSTRIAL APPLICABILITY

The compounds of the present invention have a strong antibacterial activity against not only erythromycin-sensitive bacteria but also erythromycin-resistant bacteria. Therefore, the compounds of the present invention are useful as antibacterial agents for the treatment of bacterially infectious diseases in human beings and animals (including farm animals).

CLAIMS

1. An erythromycin A derivative represented by the formula:



wherein n is an integer of 1 to 7,

$R^1$ is a group represented by the formula:

$$-SO_2N(-R^7)-R^8$$

wherein $R^7$ is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a phenyl group, a phenyl group substituted by a nitro group or an alkoxy group having 1 to 3 carbon atoms, a pyridyl group, a pyridyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a halogen atom; an alkoxy group having 1 to 3 carbon atoms; a nitro group, an amino group; a cyano group and an amino group substituted by an alkyl group having 1 to 6 carbon atoms, a quinolyl group, or a quinolyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a halogen atom; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group and an amino group substituted by an alkyl group having 1 to

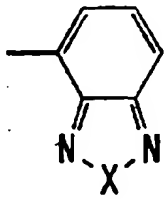
6 carbon atoms, $R^8$ is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, or

a group represented by the formula:

$$-N-(R^{10})SO_2R^9$$

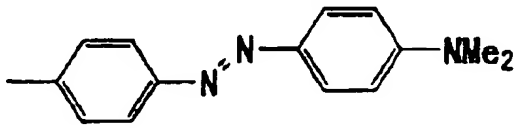
wherein $R^9$ is an alkyl group having 1 to 6 carbon atoms, a dibenzofuranyl group, a thienyl group, a thienyl group substituted by a group selected from the group consisting of a pyridyl group; an isoxazolyl group; a pyrimidinyl group and a pyrimidinyl group substituted by an alkoxy group having 1 to 6 carbon atoms or an alkylthio group having 1 to 6 carbon atoms, an isoxazolyl group, an isoxazolyl group substituted by 1 or 2 alkyl groups having 1 to 6 carbon atoms, an imidazolyl group, an imidazolyl group substituted by 1 to 3 alkyl groups having 1 to 6 carbon atoms, a benzothienyl group, a benzothienyl group substituted by 1 to 5 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms and a halogen atom, a thiazolyl group, a thiazolyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; an amino group and an acetamino group, an imidazo[2,1-b]thiazolyl group, an imidazo[2,1-b]thiazolyl group substituted by 1 to 3 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms and a halogen atom, a phenylalkyl group having 7 to 10 carbon atoms, a quinolyl, a pyridyl, a naphthyl group, a naphthylalkyl group having 11 to 15 carbon atoms, a dimethylaminonaphthyl group, a group represented by the

formula:



wherein X is -O- or -S-,

a group represented by the formula:



a phenyl group, a phenyl group substituted by 1 to 5 members selected from the group consisting of a hydroxyl group; a methylsulfonyl group; an alkyl group having 1 to 6 carbon atoms; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group; a dimethylamino group; an acetylamino group; a pyridyl group; a trifluoromethyl group; a trifluoromethoxy group and a halogen atom, a pyridyl group, a pyridyl group substituted by 1 or 2 members selected from the group consisting of a hydroxyl group; an alkyl group having 1 to 6 carbon atoms; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano group; a dimethylamino group; an acetylamino group; a pyridyl group; a trifluoromethyl group; a trifluoromethoxy group and a halogen atom, a quinolyl group, or a quinolyl group substituted by 1 or 2 members selected from the group consisting of a hydroxyl group; an alkyl group having 1 to 6 carbon atoms; an alkoxy group having 1 to 3 carbon atoms; a nitro group; an amino group; a cyano

group; a dimethylamino group; an acetylamino group; a pyridyl group; a trifluoromethyl group; a trifluoromethoxy group and a halogen atom, and $R^{10}$ is a hydrogen atom or an alkyl group having 1 to 6 carbon atoms,

$R^2$ is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or a cinnamyl group,

$R^3$ is a group represented by the formula:

$$-OCO-CH_2-R^{11}$$

a group represented by the formula:

$$-OCO-R^{11}$$

a group represented by the formula:

$$-OCO-NH-R^{11}$$

a group represented by the formula:

$$-O-R^{11}$$

or a group represented by the formula:

$$-OCO-O-R^{11}$$

wherein $R^{11}$ is a pyridylmethyl group, a methylthiomethyl group, a quinolyl group, a phenyl group, a phenyl group substituted by 1 to 5 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a nitro group; an alkoxy group having 1 to 3 carbon atoms and a halogen atom, a pyridyl group, or a pyridyl group substituted by 1 or 2 members selected from the group consisting of an alkyl group having 1 to 6 carbon atoms; a nitro group; an alkoxy group having 1 to 3 carbon atoms and a halogen atom,

$R^4$ is a hydrogen atom, or $R^3$ and $R^4$ together form an oxo

group, and

$R^5$ and $R^6$ are the same or different, and are each a hydrogen atom or an alkyl group having 1 to 6 carbon atoms, or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising an effective amount of the erythromycin A derivative or the pharmaceutically acceptable salt thereof according to Claim 1.

3. An antibacterial preparation comprising the erythromycin A derivative or the pharmaceutically acceptable salt thereof according to Claim 1 as an effective component.

4. A method for the treatment of a bacterially infectious disease which comprises administering a pharmaceutically effective amount of the erythromycin A derivative or the pharmaceutically acceptable salt thereof according to Claim 1 to a patient.

5. Use of the erythromycin A derivative or the pharmaceutically acceptable salt thereof according to Claim 1 for the treatment of a bacterially infectious disease.

# INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/JP 98/04876

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H17/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP 0 596 802 A (ROUSSEL UCLAF) 11 May 1994<br>see the whole document<br>--- | 1-5 |
| A | WO 97 31929 A (ROUSSEL UCLAF ;AGOURIDAS CONSTANTIN (FR); CHANTOT JEAN FRANCOIS (F)<br>4 September 1997<br>see the whole document<br>----- | 1-5 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 1 February 1999 | 12/02/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Scott, J |

1

# INTERNATIONAL SEARCH REPORT

Ir. .national application No.
PCT/JP 98/04876

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

information on patent family members

Interm al Application No
PCT/JP 98/04876

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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